Removing sites 23 and 24 results in similar proportions of reasons for failure across the three arms of study as well as similar proportions of reassignment by the BMS monitor. The total number of patients with discrepancies was 25 (60% of 42) minus patients from sites 23 and 24.

Relapses

Seven patients with a clinical response of cured at the Day +7 to +14 visit relapsed with symptoms consistent with AECB at the extended follow-up visit, Day +21 to +28. The overall cure rate at the end of study was 88% in the 5-day gatifloxacin arm and 87% in the 7-day gatifloxacin arm, and 87% in the clarithromycin arm. Three patients, one on each arm, had pathogens cultured from sputum at the time of relapse (one with *S. aureus*, one with *S. pneumoniae* and *P. fluorescens*, and the last with *H. influenzae*). Two pathogens, *S. aureus* and *S. pneumoniae* were pre-treatment organisms.

Table 24: Clinical Response, Clinically Evaluable Patients (+23/24, Applicant's Analysis)

	Number of Patients (%)		
Clinical Response	5 D Gati (N=151)	7D Gati (N=154)	Clarithro (N=163)
Cure at the TOC visit	135 (89)	136 (88)	145 (89)
Late Follow-up Obtained	131 (97)	136 (100)	145 (100)
Sustained cure	129 (98)	134 (99)	142 (98)
Relapse	2 (2)	2 (1)	3 (2)
Cure Rate at End of Study	133/151 (88)	134/154 (87)	142/163 (87)
WITHOUT sites 23 and 24			
Cure Rate at End of Study	84/97 (87)	85/102 (83)	85/101 (84)

MO COMMENT: The original clinically evaluable patient clinical response rates do not change to any significant degree when the relapse patients are accounted for across the three arms. Removing patients from sites 23 and 24 still results in similar cure rates across the three arms.

New Infections

Fourteen patients (3%) developed new infections. The time period included on-study and extended to 30 days after the last dose of study therapy.

Table 25: New Infections; All Treated Patients (Applicant's Analysis)

	Number of Patients (%)		
Diagnosis	5D Gati (N=174)	7D Gati (N=175)	Clarithro(N=178)
Sinusitis	3 (2)	4 (2)	–
Influenza	–	1 (<1)	1 (<1)
Urinary Tract Infection	–	–	2 (1)
Oral candidiasis	1 (<1)	–	–
Varicella zoster	–	1 (<1)	–
Herpes labialis	2 (1)	–	–

MO COMMENT: The number of new infections was low and comparable between the 3 groups, with no life-threatening infections noted. It is interesting to note however, that all 7 of the sinusitis infections were in the two gatifloxacin treated arms. It is unclear what to make of this.

Safety Evaluation

All Adverse Clinical Events

Forty percent (212) of the All Treated Patients experienced one or more adverse clinical events. Adverse clinical events taken together were less in the 5-day gatifloxacin arm (34%) than for those in either the 7-day gatifloxacin or clarithromycin arms (43% for both arms). However, the frequencies of adverse events attributed to study drugs were not different between the three arms. The most frequent events overall were gastrointestinal intolerance (mainly attributed to drug) and respiratory symptoms (mainly attributed to underlying illness).

Drug-related Adverse Clinical Events

Similar frequencies of adverse events among the three arms (27% of patients in the 5-day gatifloxacin arm and 28% of patients in both the 7-day gatifloxacin and clarithromycin arms) were considered to be drug-related according to the investigators. Diarrhea, nausea and dry mouth were the most frequent drug-related events reported in all three groups. Taste perversion was more prevalent in the clarithromycin group. In all groups, the majority of events were reported as mild or moderate in severity. There were eight adverse events reported as severe, two each in the two gatifloxacin arms and four in the clarithromycin arm. In the 5-day gatifloxacin arm, one patient had severe nausea and another patient had increased sensitivity of the eyes to light. In the 7-day gatifloxacin arm, one patient had severe dry mouth and another patient had severe diarrhea. Only the patient with the diarrhea out of these four patients discontinued therapy due to the adverse event.
All the adverse events resolved over time. In the clarithromycin arm, four patients experienced seven severe adverse events. One patient developed a headache and taste perversion. Another patient experienced severe taste perversion only. Patient three experienced severe abdominal pain. These three patients were able to complete their study medication and their adverse events resolved over time. The last patient experienced three severe adverse events, which included diarrhea, nausea, and vomiting. Treatment was not needed but the study drug was discontinued and the symptoms resolved.

Table 26: All Adverse Clinical Events

Number of Patients (%):	5D Gati (N=174)			7D Gati (N=175)			Clarithro (N=178)		
Adverse Clinical Events	DR	NDR	Total	DR	NDR	Total	DR	NDR	Total
Diarrhea (7)	13 (7)	1 (<1)	14 (8)	10 (6)	–	10 (6)	11 (6)	2 (1)	13
Nausea	8 (5)	1 (<1)	9 (5)	11 (6)	1 (<1)	12 (7)	10 (6)	–	10 (6)
Increase coughing	–	8 (5)	8 (5)	–	12 (7)	12 (7)	–	5 (3)	5 (3)
Headache (6)	3 (2)	4 (2)	7 (4)	3 (2)	4 (2)	8 (5)	5 (3)	5 (3)	11
Dry mouth	7 (4)	–	7 (4)	10 (6)	–	10 (6)	6 (3)	–	6 (3)
Increased sputum	–	6 (3)	6 (3)	–	8 (5)	8 (5)	–	4 (2)	4 (2)
Dyspnea	–	6 (3)	6 (3)	–	8 (5)	8 (5)	–	5 (3)	5 (3)
Taste perversion	6 (3)	–	6 (3)	3 (2)	–	3 (2)	15 (8)	–	15 (8)
Dyspepsia	4 (2)	–	4 (2)	3 (2)	–	3 (2)	1 (<1)	1 (<1)	2 (1)
Asthenia	3 (2)	1 (<1)	4 (2)	–	–	–	–	–	–
Somnolence	4 (2)	–	4 (2)	–	–	–	–	1 (<1)	1 (<1)
Chest Pain	–	3 (2)	3 (2)	–	10 (6)	10 (6)	–	2 (1)	2 (1)
Constipation	3 (2)	–	3 (2)	–	–	–	3 (2)	–	3 (2)
Tremor	2 (1)	1 (<1)	3 (2)	–	–	–	2 (1)	–	2 (1)
Sinusitis	–	3 (2)	3 (2)	–	3 (2)	3 (2)	–	–	–
Abnormal Breath Sounds	–	2 (1)	2 (1)	–	3 (2)	3 (2)	–	3 (2)	3 (2)
Dizziness	1 (<1)	1 (<1)	2 (1)	7 (4)	–	7 (4)	1 (<1)	2 (1)	3 (2)
Malaise	–	2 (1)	2 (1)	–	4 (2)	4 (2)	1 (<1)	1 (<1)	2 (1)

Rhinitis	–	2 (1)	2 (1)	1 (<1)	7 (4)	8 (5)	–	3 (2)	3 (2)
Abdominal pain	1 (<1)	–	2 (1)	1 (<1)	–	1 (<1)	3 (2)	–	3 (2)
Pain	–	2 (1)	2 (1)	1 (<1)	2 (1)	3 (2)	1 (<1)	1 (<1)	2 (1)
Nervousness	1 (<1)	–	1 (<1)	2 (1)	–	2 (1)	3 (2)	1 (<1)	4 (2)
Vomiting	1 (<1)	–	1 (<1)	5 (3)	–	5 (3)	1 (<1)	–	1 (<1)
Insomnia	–	–	–	1 (<1)	–	1 (<1)	3 (2)	1 (<1)	4 (2)
Flatulence	–	–	–	–	–	–	4 (2)	–	4 (2)
Patients with Any ACE	**47(27)**	**13(7)**	**60(34)**	**49(28)**	**26(15)**	**76(43)**	**50(28)**	**24(13)**	**76(43)**

Table 27A: Drug-related Adverse Clinical Events: All Treated Patients

Number of Patients (%):	5D Gati (N=174)			7D Gati (N=175)			Claritho (N=178)		
Adverse Clinical Events	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Diarrhea	11 (6)	2 (1)	–	5 (3)	4 (2)	1 (<1)	6 (3)	4 (2)	1 (<1)
Nausea	6 (3)	1 (<1)	1 (<1)	9 (5)	2 (1)	–	8 (4)	1 (<1)	1 (<1)
Dry mouth	7 (4)	–	–	6 (3)	3 (2)	1 (<1)	5 (3)	1 (<1)	–
Taste perversion	6 (3)	–	–	3 (2)	–	–	10 (6)	3 (2)	2 (1)
Dyspepsia	3 (2)	1 (<1)	–	2 (1)	1 (<1)	–	1 (<1)	–	–
Somnolence	3 (2)	1 (<1)	–	–	–	–	–	–	–
Headache	1 (<1)	2 (1)	–	2 (1)	1 (<1)	–	2 (1)	2 (1)	1 (<1)
Asthenia	2 (1)	1 (<1)	–	–	–	–	–	–	–
Constipation	2 (1)	1 (<1)	–	–	–	–	1 (<1)	2 (1)	–
Tremor	2 (1)	–	–	–	–	–	1 (<1)	1 (<1)	–
Dizziness	–	1 (<1)	–	6 (3)	1 (<1)	–	1 (<1)	–	–
Vomiting	1 (<1)	–	–	3 (2)	2 (1)	–	–	–	1 (<1)
Abdominal pain	1 (<1)	–	–	1 (<1)	–	–	2 (1)	–	1 (<1)
Eructation	1 (<1)	–	–	–	1 (<1)	–	2 (1)	–	–
Nervousness	–	1 (<1)	–	1 (<1)	1 (<1)	–	2 (1)	1 (<1)	–
Flatulence	–	–	–	1 (<1)	1 (<1)	–	–	4 (2)	–
Vaginitis	–	–	–	–	2 (1)	–	1 (<1)	2 (1)	–
Abnormal dream	–	–	–	–	–	–	2 (1)	–	–
Insomnia	–	–	–	1 (<1)	–	–	1 (<1)	2 (1)	–
Patients with Any DR-ACE	**33(19)**	**12(7)**	**2(1)**	**33(19)**	**14(8)**	**2(1)**	**31(17)**	**15(8)**	**4(2)**

All adverse clinical events occurring in > 1% in any of the 3 treatment groups.
Vaginitis was calculated on female patients only, not the entire study population.

MO COMMENT: *Most adverse events in the gatifloxacin group were non-serious in nature. Diarrhea was most frequent with the 5-day gatifloxacin arm whereas nausea was most frequent in the 7-day gatifloxacin arm. Taste perversion was the most frequent adverse event in the clarithromycin group. There were more events of dizziness in the 7-day gatifloxacin arm. Quinolone-class related events, namely phototoxicity, tendinitis, seizures, and cardiac symptoms, were not encountered.*

Removing sites 23 and 24 did not change the proportion of adverse event frequencies for the three arms of study. Again, less adverse clinical events were reported overall for the 5-day gatifloxacin group (35%) than the 7-day gatifloxacin group (49%) or the clarithromycin group (47%) and similar frequencies were found between all three arms if only the drug-related events were isolated (25% for 5-day gatifloxacin, 36% for 7-day gatifloxacin, and 28% for clarithromycin).

All 8 patients with severe drug-related adverse clinical events remain in the retabulated patient population.

Table 27B: Drug-related Adverse Clinical Events: All Treated Patients (-23/24)

Number of Patients (%):	5D Gati (N=109)			7D Gati (N=113)			Clarithro (N=108)		
Adverse Clinical Events	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Diarrhea	7 (6)	1 (<1)	--	3 (3)	3 (3)	1 (<1)	3 (3)	3 (3)	1 (<1)
Nausea	1 (3)	1 (<1)	1 (<1)	3 (3)	1 (<1)	--	3 (3)	--	1 (<1)
Dry mouth	3 (3)	--	--	--	3 (3)	1 (<1)	--	1 (<1)	--
Taste perversion	2 (2)	--	--	1 (<1)	--	--	3 (3)	3 (3)	2 (2)
Dyspepsia	1 (<1)	1 (<1)	--	1 (<1)	1 (<1)	--	--	--	--
Somnolence	1 (<1)	1 (<1)	--	--	--	--	--	--	--
Headache	1 (<1)	2 (2)	--	1 (<1)	1 (<1)	--	2 (2)	1 (<1)	1 (<1)
Asthenia	1 (<1)	1 (<1)	--	--	--	--	--	--	--
Constipation	--	1 (<1)	--	--	--	--	1 (<1)	2 (2)	--
Tremor	2 (2)	--	--	--	--	--	1 (<1)	1 (<1)	--
Dizziness	--	1 (<1)	--	3 (3)	1 (<1)	--	--	--	--
Vomiting	1 (<1)	--	--	3 (3)	1 (<1)	--	--	--	1 (<1)
Abdominal pain	1 (<1)	--	--	1 (<1)	--	--	2 (2)	--	1 (<1)
Eructation	1 (<1)	--	--	--	1 (<1)	--	2 (2)	--	--
Nervousness	--	1 (<1)	--	1 (<1)	1 (<1)	--	2 (2)	1 (<1)	--
Flatulence	--	--	--	--	1 (<1)	--	--	4 (4)	--
Vaginitis	--	--	--	--	2 (3)	--	1 (2)	2 (3)	--
Abnormal dream	2 (2)	--	--	--	--		2 (2)	--	--
Insomnia	--	--	--	1 (<1)	--	--	1 (<1)	2 (2)	--
Patients with Any DR-ACE 4(4)	**14(13)**	**11(10)**	**2(2)**	**14(12)**	**13(12)**	**2(2)**	**14(13)**	**12(11)**	

All adverse clinical events occurring in > 1% in any of the 3 treatment groups.
Vaginitis was calculated on female patients only, not the entire study population.

Deaths and Serious Adverse Events

No deaths were reported from the start of dosing up to 30 days after the last dose.

There were 13 serious adverse events in 8 (1.5%) patients (3 in the 5-day gatifloxacin arm, 3 in the 7-day gatifloxacin arm, and 2 in the clarithromycin arm) which were considered to be related to study medication by the investigators. All 8 patients had medically significant events leading to hospitalizations. The longest hospitalization was 13 days in a patient who needed mechanical ventilation due to respiratory failure. Six patients (2 in 5-day gatifloxacin arm, 2 in 7-day gatifloxacin arm, and 2 in the clarithromycin arm) had serious adverse events that were respiratory in nature (hospitalizations for pneumonia, asthma, worsening exacerbation, and one patient with hypoxia related to COPD coupled with back pain from compression fracture of the 7th thoracic vertebrae). One other patient in the 5-day gatifloxacin arm was hospitalized for abdominal pain and rectal bleeding 3 days after the completion of therapy. The last patient was in the 7-day gatifloxacin arm. His serious adverse event was hyperglycemia (433 mg/dL) noted on end-of-therapy bloodwork. This patient received a diagnosis of diabetes mellitus at a subsequent visit.

MO COMMENT: *The brief case summaries of these eight patients (034-244, 041-346, 051-553, 005-029,007-039, 007-421, 007-046, and 053-574) as well as their case report forms were reviewed. The majority of serious adverse events were related to respiratory progression from underlying disease. There was a low incidence of serious adverse events and the frequencies for the three treatment groups were similar.*

Adverse Events Leading to Discontinuation of Study Therapy

Of the 527 patients who received at least one dose of either study drug, ten (2%) discontinued treatment due to adverse clinical events. Two patients in the 5-day gatifloxacin arm had 5 adverse events attributed to be wither possibly or probably related to study drug. One patient had a coincident asthma attack (patient has a history of asthma), and the other patient had central nervous system complaints (dizziness, headache, nervousness, sweating) leading to discontinuation of study drug. In the 7-day gatifloxacin treated arm, three patients had gastrointestinal symptoms (diarrhea, nausea, vomiting) which were assessed to be possibly related to study drug. The fourth patient's adverse event (bilateral dull knee pain) was also assessed to be possibly drug-related. In the clarithromycin treated group, two patients discontinued due to gastrointestinal symptoms that were assessed to be probable and certainly drug-related. The third patient discontinued due to central nervous system complaints, and the last patient discontinued mainly due to taste perversion.

MO COMMENT: The narrative summaries on these 10 patients (031-363, 037-254, 010-279, 014-830, 023-846, 041-735, 001-313, 009-055, 010-277, and 027-161)and their case report forms were reviewed. I agree with the assessments as written by the applicant. Very little percentage of the study population discontinued drug. Gastrointestinal and central nervous system events were the main reasons leading to discontinuation. The 5-day gatifloxacin, 7-day gatifloxacin, and the clarithromycin arms were comparable with respect to the frequency of discontinuations due to adverse events. From this study, it appears that gatifloxacin has a favorable clinical adverse event profile.

Removing sites 23 and 24 affects one patient out of the ten discontinuations. This one patient was in the 7-day gatifloxacin arm and had gastrointestinal adverse events possibly attributed to study drug.

Laboratory Test Results

Patients with Normal Pre-treatment Values

Very few patients with normal baseline values developed abnormal laboratory test results during or post-treatment. There were no appreciable differences between the treatment arms. The majority of the abnormalities were Grade 1 with the most frequent lab tests affected being hemoglobin, electrolytes, and liver enzymes in the three treatment groups. Hyponatremia was the most frequent abnormality in all three treatment arms. Grade 1 hyponatremia was noted in 26 (18%) of 143 tested patients in the 5-day gatifloxacin arm, 25 (18%) of 136 tested patients in the 7-day gatifloxacin arm, and 25 (16%) of the 153 tested in the clarithromycin arm. Grade 1 AST abnormalities were noted in 8 (6%) of 141 tested patients in the 5-day gatifloxacin arm, 14 (10%) in the 140 tested patients in the 7-day gatifloxacin arm, and 16 (11%) of the 146 patients tested in the clarithromycin arm. All the Grade II abnormalities in the three arms were 1% or less except for neutrophil abnormality in the clarithromycin arm at 2%. There were 4 patients with Grade III abnormality in the gatifloxacin treated groups. The one patient in the 5-day gatifloxacin arm had AST levels elevated to 228 U/L from baseline normal values. The patient had no physical history that would explain the elevated AST levels and no follow-up values were obtained. Two patients in the 7-day gatifloxacin group had Grade III hypochloremia and the last patient had neutrophil count worsen to Grade III abnormal level. No Grade III test elevations were observed for patients on clarithromycin. No Grade IV elevations were reported for any treatment group.

Patients with Abnormal Pre-treatment Values

Patients who had abnormal (Grade 1, 2, or 3) pre-treatment laboratory values occasionally experienced worsening to a higher grade during or post-treatment. In the 5-day gatifloxacin arm, one patient worsened to a Grade 3 abnormality and another to a Grade 4. The first patient's AST levels rose from 130 U/L at baseline to 186U/L on Day 3. This level was evaluated on Day +7 as a Grade 2 (148 U/L). On the 7-day gatifloxacin arm, there was just one patient who developed a Grade 3 abnormality with a chloride level of 87 mEq/L. On the clarithromycin arm, two patients that initially had abnormal labs showed worsening lab values reaching Grade 3 abnormality. One patient had depressed levels of neutrophils at baseline worsened to Grade 3 levels but had

a complete improvement by Day +7. This patient and the other patient in the clarithromycin-treated arm both had Grade 3 abnormal liver function (AST) values. Both patient's AST values came down to Grade I values by Day +7.

MO COMMENT: *Gatifloxacin appears to have a favorable adverse event profile in terms of laboratory parameters. Glucose levels were not measured in this study. Abnormalities in liver function tests were not severe, and the combination of elevated transaminase and hyperbilirubinemia were not measured.*

Conclusions

The applicant's overall conclusions were

1) "results of this study indicate that gatifloxacin 400 mg daily is safe and effective when given for 5 days for the treatment of acute exacerbation of chronic bronchitis"

MO COMMENT: *Data in this study were well represented in tables and appendices in hard copy and electronic format, which allowed easy derivation for the reviewers' own analysis. Individual patient data were well documented on Case Report Forms, as shown by a thorough review of 10% of the forms. The request for retabulated data without patients from sites 23 and 24 was promptly attended to and the response packet well organized and meaningful. The primary efficacy analysis between the 5 day gatifloxacin and the comparator clarithromycin are well within the lower boundary of the 95% Confidence Interval of −15%. This equivalence in efficacy has shown consistency across different treated populations including the All Treated and Clinically Evaluable patients.*

2) " The drug demonstrated a favorable safety profile and clinical bacteriologic efficacy in a highly representative cohort of patients with this disease compared to clarithromycin. Efficacy was documented in microbiologically evaluable patients, with high rates of eradication of *H. influenzae, M. catarrhalis,* and *S. pneumoniae*. Eradication of the other respiratory pathogen, *H. parainfluenzae* and *S. aureus*, also documented efficacy"

MO COMMENT: *The drug demonstrates a favorable safety profile in this study. Certainly, there are no appreciable differences in the safety profile when compared to the active control. However, safety will be further examined through the review of the integrated safety data. The safety data from this study does not support one of the applicant's rationale that using a shorter course of antibiotic therapy will "result in fewer side effects". The incidence of adverse events was similar for 5-day and 7-day gatifloxacin arms.*

Inclusion criteria for this study utilized the Anthonisen classification, which has not been validated to capture the "highly representative cohort of patients with AECB". The classification system is entirely clinical, and does not make any adjustments for factors such as older age, need for baseline respiratory medications, pulmonary function tests attesting to chronic obstructive lung disease, etc. Consequently, when the characteristics of the study population are examined, this reviewer has observed that there was a wide mix of patients. Patients ranged from 18 year old smokers not on any chronic medications having smoke-related cough, to 85 year old medically fragile chronic obstructive pulmonary disease patients routinely treated with oxygen therapy and respiratory medications. It is the latter type of patient developing an acute bacterial respiratory infection who would most benefit from broad-spectrum antimicrobial therapy. It was fortunate that the modifications needed for data analysis (namely excluding patients from sites 23 and 24) resulted in excluding the subset of patients (with significant patient numbers) who were younger and less ill at baseline (those patients who we would consider NOT "highly representative cohort of patients with this disease").

This reviewer agrees that this study demonstrates equivalent bacteriologic efficacy when compared to clarithromycin. Data regarding microbiologic efficacy were supportive of effectiveness against the major pathogens involved in AECB, namely H. influenzae, M. catarrhalis, and S. pneumoniae, but also against H. parainfluenzae and S. aureus. Because significant numbers of pathogens were removed due to data analysis without sites 23 and 24, the absolute numbers for these pathogens are quite small and will need to be examined in conjunction with pathogen data from the second trial.

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APPENDIX #2: APPLICANT'S STUDY AI420-065

A Randomized, Double-Blind, Multi-center, Comparative Study of Gatifloxacin Versus Azithromycin in the Treatment of Acute Exacerbation of Chronic Bronchitis (AECB)

Table of Contents

Gatifloxacin (Tequin®) is an 8-methoxy fluoroquinolone that is currently approved for a 7-10 day course treatment of acute exacerbation of chronic bronchitis. In this current supplemental NDA, the sponsor (Bristol-Myers Squibb Company) is seeking approval for 5 day duration of therapy for the treatment of acute exacerbation of chronic bronchitis. The dose proposed is 400 mg once a day (both intravenous or oral), and the age group is 18 years and above inclusive. This is the second of two pivotal trials submitted to support the approval of these efficacy supplements.

Rationale/Objective

The rationale given for seeking a 5 day regimen for the AECB indication was that shorter-course therapy would increase compliance and convenience, result in fewer side effects, lower costs, and decrease bacterial resistance. The applicant also pointed out that Avelox (Moxifloxacin – Bayer) was granted approval for 5day treatment of AECB.

The primary objective of this study (al420-065) was to demonstrate equivalent clinical efficacy of 5 day gatifloxacin treatment in AECB relative to a standard 5 day regimen of Azithromycin,

The secondary objectives were to evaluate the safety of gatifloxacin relative to the standard regimen of Azithromycin and demonstrate microbial eradication rates and responses for the most common pathogens causing AECB.

Design

This trial was a randomized, comparative, double-blind, "double-dummy", multicenter study that would assess the efficacy of gatifloxacin, 400 mg PO daily for 5 days in comparison to a standard 5 day regimen of azithromycin (500 mg PO on Day 1 followed by 250 mg PO on Days 2-5) for the treatment of adults with AECB. Forty-five investigators in the US were recruited and 33 sites enrolled patients. Patients were stratified by corticosteroid use (either inhaled or systemic) on the day of randomization. The target enrollment was 282 patients with a 1:1 randomization to either study or comparator drug. Duration of the clinical phase was approximately 5 weeks. The sample size was determined using a cure rate of 85% for both treatment groups. Assuming equivalence in response rates between the two treatment groups and 90% power to rule out a maximum difference of 20%, 120 evaluable patients per arm were needed. With an estimated evaluability rate of 85%, enrollment was targeted at 282 based on a two-sided Type I error rate of 0.05.

MO COMMENT: *This trial attempts to establish equivalence of 5 day gatifloxacin treatment to an approved 5 day treatment drug for the indication of AECB. The study design uses an active control drug and a random assignment of patient to the investigational drug and the active control drug groups in a double-blind fashion. This is the preferred design according to the IDSA/FDA "Guidelines For The Evaluation of Anti-Infective Drug Products". Unlike the Trial 1 (study 064) where a large percentage of subjects were enrolled from a couple of sites, enrollment numbers in this second trial was more evenly distributed throughout the sites. The 33 sites with patients accrued were from 20 different states throughout the USA .*

Protocol

Study Population

Inclusion and Exclusion

For inclusion, patients with a history of chronic bronchitis (i.e. productive cough on most days for at least three consecutive months in two consecutive years) and a diagnosis of AECB had to meet all of the following criteria:

1) Eighteen years of age or older
2) Clinical diagnosis of acute exacerbation of chronic bronchitis, defined as:
   - The presence of purulent sputum confirmed by Gram stain examination [>25 polymorphonuclear leukocytes (PMN) per low power field (LPF)]
   - The presence of all of the following signs and symptoms:
     - increase cough and/or dyspnea
     - increased sputum volume
     - increased sputum purulence
3) For women of childbearing potential:
   - A negative urine pregnancy test within two days prior to enrollment
   - A commitment to use an effective method of contraception from the start of study treatment to use an effective method of contraception from the start of study treatment until the end of their participation in the study
4) Written informed consent (from patient or their guardians) before any study procedure were performed

Patients were excluded if they met any of the following criteria within 2 days prior to randomization:

1) Pregnant or lactating
2) History of significant hypersensitivity reaction to any quinolone or macrolide/azalide antibiotic
3) Received a systemic antibiotic therapy within five days prior to randomization, or were likely to require other systemic antibiotic(s) concomitantly
4) Diagnosis of pneumonia confirmed by the presence of pulmonary infiltrates on a chest x-ray
5) Previously diagnosed disease(s) of immune function (e.g. AIDS or history of clinical manifestations of HIV infection, neutrophil count $<1000/mm^3$)
6) Previously diagnosed condition that would tend to mimic or complicate the course and evaluation of the infectious process
7) Known renal insufficiency (i.e. creatinine clearance $\leq$ 40 mL/min of requiring renal dialysis)
8) Current clinically significant hepatic disease (i.e. aspartate amino transferase [AST] and/or alanine amino transferase [ALT] and/or total bilirubin > 3 times the upper limit of normal)
9) Malabsorption syndromes or other gastrointestinal disturbances that would affect drug absorption
10) Previous treatment in any gatifloxacin AECB clinical trials

MO COMMENT: *Inclusion and exclusion criteria were clearly identified prior to initiation of the study and are in line with the original NDA for AECB. Only patients with exacerbation Type 1 (see below) were included in this study. This is different from study 064 where both Type 1 and Type 2 were included. Also different from study 064 was randomization by corticosteroid use, which included both inhaled and systemic steroids. The exclusion of patients with AIDS, renal insufficiency, and hepatic disease makes it difficult to predict safety and efficacy in these population groups.*

Exacerbation type at entry was determined according to the following criteria established by Anthonisen, et al.

- Type I: increased dyspnea, increased sputum volume and increased sputum purulence
- Type II: any two of the three symptoms of Type I
- Type III: any one of the three symptoms of Type I

MO COMMENT: *Anthonisen et al. used the above criteria in an AECB study that was published in the Annuals of Medicine in 1987. His inclusion criteria required that all patients enrolling into the trial have a baseline pulmonary obstructive disease as defined by $FEV_1 < 70\%$ and be no younger than 35 years of age. This is very different than what was done in this trial. The only requirement for entry into this protocol was to have "productive cough on most days for at least three consecutive months in two consecutive years". There were no objective measurements to ensure that patients being enrolled into the protocol had true baseline pulmonary disease.*

Patients received gatifloxacin 400 mg PO once a day for 5 days or azithromycin 500 mg PO Day 1 followed by 250 mg PO Day 2-5 with placebo in "double dummy" fashion. There were no provisions for dose modification. Patients were asked to fill in a medication diary to encourage compliance.

MO COMMENT: *The dose used in this study for the active control comparator azithromycin is the currently labeled dose for the treatment of AECB.*

Patients were excluded it they had received antibiotic therapy within 5 days before enrollment. Other antimicrobial agents, such as antivirals and antifungals, were permitted pre-treatment. Adjunctive measures, such as oral or topical decongestants, antihistamines, and intranasal steroids, were permitted during and post-treatment as needed by the patient. In addition, concomitant or post-treatment non-drug therapies, such as postural drainage or oxygen were allowed. Investigators were permitted to discontinue study drug and remove patients from the study for the following reasons:

- An adverse event
- Persistence or worsening of signs and symptoms of the acute infection after three days of study drug therapy
- An intercurrent illness
- Patient's decision not to participate any further
- Investigator's decision that discontinuation was in the patient's best interest
- A female patient with a positive pregnancy test during study drug therapy (immediate discontinuation)
- Investigator's decision that discontinuation was in the patient's best interest
- Decision of the sponsor to terminate the study (at some or all sites)

Patients with one or more study drug-resistant pre-treatment pathogens were removed from the study if the investigator felt it was in their best interest. Patients whose condition had not improved or had worsened after 3 days of study drug therapy (early treatment failures) were removed from the study. These patients had the same clinical and laboratory procedures performed as those specified for the past-treatment visit scheduled for Day +7 to Day +14 before starting alternative antibiotic therapy.

Clinical and bacteriologic responses to gatifloxacin therapy were to be assessed at the Day +7 to Day +14 post-treatment visit, or earlier for those who discontinued prematurely. Clinical response to study therapy was based upon the signs and symptoms of the acute infection; the bacteriologic response for each pre-treatment pathogen was based on culture results or, if there was no source to culture, the clinical assessment at the Test of Cure (TOC) visit. Relapse was evaluated at the Day +21 to Day +28 extended follow-up assessment.

Patient Assessments

Patient assessments were scheduled to occur as follows (Table 2):

- Pre-treatment (within 48 hours before dosing) office/clinic visit
- End of treatment (Day +1 to Day +3) telephone contact (office/clinic visit for further evaluation if not clinically improved)
- Test-of-Cure (Day +7 to Day +14) office/clinic visit
- Follow-up (Day +21 to Day +28) office/clinic visit

Table 1: Schedule of Patient Assessments

Procedure	Pre-treatment (Within 2 days prior to dosing)	End of Treatment[a] (Days +1 to +3)	Post-Treatment (Days + 7 to +14)	Follow-up (Days + 21 to +28)
Screening[c]	X	--	--	--
Chest X-Ray	X	--	X	--
Medical History	X	--	--	--
Physical Exam	X	--	X	--
Vital Signs	X	--	X	--
Clinical Evaluation	X	X	X	X
Laboratory Tests	X	--	X	--
Pharyngeal Swabs	X		X	X
Sputum Smear and Evaluation	X	--	X[b]	X[b]
Sputum Culture	X	--	X[b,c]	X[b.c]
Clinical Response Determination	--	--	X	--
Bacteriologic Response Determination	--	--	X	--
Assess Adverse Events	--	X	X	X
Assess Medication Use	--	X	X	--
Pregnancy Test	X	--	X	--
Subject Diary/Relapse Diary	--	X[d]	X[e]	--

[a] Telephone contact. If patient not clinically improved, office visit to be scheduled for further evaluation

[b] If sputum production persists.

[c] If a purulent sputum is obtained

[d] Subject diary card is completed daily until the TOC visit (Day +7 to +14)

[e] Relapse diary distributed

A central laboratory performed all laboratory procedures, including appropriate cultures. Investigators performed initial Gram stain procedures on site to expedite determination of sputum purulence and, therefore, patient eligibility. The Central laboratory performed an independent sputum Gram stain and would overread the smear provided by the site. Results from the central laboratory's Gram stain and their overread were made available to the Investigator within 24-48 hours of a patient's enrollment. A qualifying result (i.e. >25 PMN/LPF) from either of the two sputum Gram stains was sufficient for the patient's continued participation in the study. If both sputum Gram stain results showed <25 PMN/LPF, the patient was to continue on study up to the TOC visit, following which they were considered off study.

All nasopharyngeal swabs and sputum specimens were plated semi-quantitatively for aerobic growth, and all potential pathogens isolated were tested for susceptibility to gatifloxacin and azithromycin. Hematology,

serum chemistry, and urinalysis tests included: White blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, amylase, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, and microscopic urinalysis. A urine pregnancy test was performed on all women of childbearing potential. Positive urine pregnancy tests were confirmed with a serum-based pregnancy test. All pre-treatment procedures were performed within two days prior to the start of study medication. Symptom diaries were distributed at this time.

In the three day period immediately following the end of therapy (i.e., Day +1 to Day +3, inclusive), patients were contacted by telephone and queried about the clinical symptoms of infection, the occurrence of adverse events, and compliance with the dosing regimen. If a patient's signs and symptoms had not returned to baseline, or if clear clinical improvement had not occurred, the patient was scheduled for an immediate office visit. Clinical and laboratory procedures planned for the post-treatment visit scheduled for Day +7 to Day +14 were performed at that time.

Between seven and fourteen days post-treatment (i.e., Day +7 to Day +14, inclusive), patients were evaluated in the office/clinic for clinical and bacteriologic response to study drug therapy and the occurrence of adverse clinical events. If a patient is still producing sputum, a specimen was obtained for assessment of purulence, quantitative culture and susceptibility testing. Nasopharyngeal swabs were obtained for culture and susceptibility testing as well. If a laboratory test result became abnormal or worsened from an abnormal pre-treatment level, the test was repeated at appropriate intervals until the value either returned to the pre-treatment level or stabilized. The symptom diary was to be returned at this visit.

Patients who did not receive additional systemic antibiotics were seen approximately two weeks after the post-treatment visit (i.e., Day +21 to Day +28, inclusive) to assess relapse of the acute infection. Patients were queried about the presence and severity of clinical signs and symptoms of infection, the ingestion of any antibiotics since the last office/clinic visit, and the occurrence of adverse clinical events. If increased sputum production persisted, a sputum sample was assessed for purulence and, if purulent, was submitted for bacteriologic culture and susceptibility testing. Nasopharyngeal swabs for culture and susceptibility testing were collected at this time as well.

MO COMMENT: Routine patient monitoring was at a minimum in terms of frequency of visits. Unlike study 064, patients were not required to be examined physically at all during treatment or at end of treatment. The first time subjects were routinely examined in person was at the TOC visit. Rather, telephone contacts were the mainstay of patient follow-up. Patients were seen in person if clinically indicated. Laboratory tests were adequate for proper detection of toxicity. Study drug levels were not measured to verity compliance, which was only done through a patient maintained diary. Reliance on a central laboratory minimizes intersite variability and ensures consistency of test results.

Endpoints

Clinical and bacteriologic responses were determined from data at the TOC visit scheduled between Day +7 and Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit from Day +5 and Day +18, inclusive, was acceptable. Investigators assigned a clinical response to each patient and a bacteriologic response to each pre-treatment pathogen. If a patient did not have a post-treatment visit, a response was derived from any available data during or post-treatment. Each patient was assigned a clinical response of Cured, Failure, or Unable to Determine with every possible attempt at either a Cure or Failure assignment. For discrepancies between the Investigators and the BMS Medical Monitor where a consensus cannot be reached, the efficacy analyses were based on the responses assigned by the Medical Monitor.

Clinical Response

CURED at TOC

- All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, sputum purulence) have improved or returned to the patient's baseline level with the original therapy alone and without need for further antimicrobials; and
- No new signs or symptoms of acute infection were present.
- and if elevated at study entry, fever was resolved (i.e., temperature ≤ 38°C or 100.4°F)
- (Note: Baseline is defined as the patient's assessment of their typical/usual condition when free of acute infection).

FAILURE:

- New clinical signs and symptoms of acute infection appeared, or
- If present at study entry, the patient still has fever (i.e., temperature > 38°C or 100.4°F), or
- Clinical/radiological evidence of pneumonia; or
- Another antibiotic was required for treatment of this acute episode despite the resolution or improvement of signs and symptoms; or
- One or more signs and symptoms of acute infection have failed to improve.

UNABLE TO DETERMINE:

- No follow-up beyond the pre-treatment visit.

MO COMMENT: It is important to note that to be CURED, the study subject had to have all signs and symptoms related to the acute infection "improved" or "returned to baseline"> However, there were no objective measures of 'improvement" or "returned to baseline" such as pulmonary function tests, symptom scores, etc. There was no grading of the symptoms. The signs/symptoms assessments were entirely subjective, i.e. patient reporting "my cough is better" and/or investigator reporting "sputum is less purulent".

Bacteriologic Response

ERADICATED:

- The original pathogen was absent in the culture of a good quality (i.e., > 25 PMN/LPF) sputum specimen obtained at the TOC visit.

PRESUMED ERADICATED:

- The subject was not producing sputum (i.e., there was no source to culture); or
- No sputum was obtained, and the clinical response was CURED.

PERSISTED:

- The original pathogen was present in the culture of a good quality (i.e., > 25 PMN/LPF) sputum specimen obtained at the TOC visit.

PRESUMED PERSISTED:

- The subject was not producing sputum (i.e., there was no source to culture); or
- No sputum was obtained, and the clinical response was FAILURE.

UNABLE TO DETERMINE:

- The clinical response of the patient in question was designated Unable to Determine.

  (this means there was no follow-up visit beyond the pre-treatment visit)

A **by-patient bacteriologic response** was computed for each patient with at least one pathogen isolated pre-treatment. The by-patient response incorporates the bacteriologic responses for all pre-treatment sputum pathogens isolated for a patient. For example, a patient with two pre-treatment pathogens, one eradicated and one persisted, was assigned the by-patient bacteriologic response of ERAD/PERS. No distinction was made between documented and presumed responses. **Persistent Pathogens** were tested for susceptibility to both study drugs as well as to other appropriate antibiotics.

Relapse

Patients who had a clinical response of Cured at the TOC visit were evaluated for relapse at the extended follow-up assessment (Day +21 to Day +28). Relapse was defined as:

- Symptoms related to acute exacerbation of chronic bronchitis returned after initial resolution or improvement; or
- New clinical symptoms of acute bronchial infection have appeared without documentation of a new pathogen; or
- The subject received alternative antibiotic therapy because of worsened, reappearance of, or new signs and symptoms of an acute bronchial infection.

Pathogens isolated from relapsed patients were speciated and tested for susceptibility to gatifloxacin, azithromycin and other antibiotics as appropriate.

New Infections

A new infection was defined as the occurrence, at any time during or after study therapy (up to Day +30 inclusive), of one of the following:

- Isolation of any pathogen from a new site of infection, with associated clinical signs and symptoms;
- The presence of clinical signs and symptoms indicative of a new infection for which a culture would not usually be obtained (e.g., skin infection).

Pathogens isolated from patients with new infections were speciated and tested for susceptibility to gatifloxacin, azithromycin and other antibiotics as appropriate.

Safety Variables and deaths were collected between the first day of study drug treatment and 30 days after the last day of study drug treatment, inclusive.

Adverse Clinical Events

Investigators reported all adverse events to the Sponsor, along with their judgement of the causality. For the purpose of analysis, events that were certainly, probably, or possibly drug-related were grouped and categorized as "drug-related". Investigators also assessed the severity (mild, moderate, severe, or very severe) of each adverse clinical event.

Abnormal Laboratory Results

Any worsening in laboratory parameters during or post-treatment was categorized according to a severity grading scale derived from the National Cancer Institute's Common Toxicity Criteria (CTC) and the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) classification of laboratory abnormalities. Four grades of abnormality were defined (Grades 1-4), and the range of laboratory values associated with each grade was established for each test. Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the abnormal values returned to pre-treatment levels or were deemed by the investigator to be unrelated to the study medication.

***MO COMMENT**: Clinical, microbiologic, and laboratory endpoints were adequately defined prior to study initiation.*

Statistical Considerations

Data Set Descriptions
(Four Study Populations of Interest)

ALL TREATED PATIENTS: All patients who received at least one dose of study medication.

ELIGIBLE PATIENTS: All Treated Patients with a diagnosis of AECB at entry, defined as:

- A positive answer to the question "Has the patient coughed up sputum on most days for at least three consecutive months for at least two consecutive years?"
- All of the signs/symptoms of AECB at study entry: increased dyspnea and cough, increased sputum production, and increased sputum purulence.
- Having a pretreatment radiograph that did not show pneumonia
- Evidence of purulence from an adequate pre-treatment sputum sample (>25 PMN/LPF) obtained within 2 days prior to start of treatment

CLINICALLY EVALUABLE PATIENTS: All Eligible Patients who

- Received at least 4 days of study medication (at least 3 for failures)
- Had a post-treatment clinical assessment within the Day +5 to Day +18 window for the TOC visit (except for failures)
- Did not receive a systemic antibacterial agent between the time of the pre-treatment visit and the post-treatment assessment

MICROBIOLOGICALLY EVALUABLE PATIENTS: All Clinically Evaluable Patients who had at least one pathogen isolated pre-treatment non-resistant (susceptible and intermediate) pre-treatment to either study drug.

***MO COMMENT**: The 4 datasets correspond to the definitions for the indication of AECB in the initial gatifloxacin NDA application that was approved for 7-10 days duration. FDA clinical efficacy analysis will utilize the following evaluability criteria which is in keeping with using antibiotic therapy to treat acute exacerbation of chronic bronchitis. The modified intent to treat group (MITT) and the modified clinically evaluable (MCE) groups will be analyzed to verify the efficacy results obtained by the applicant. MITT evaluable population will include all patients enrolled EXCLUDING those who*
1) did not have purulent pre-treatment sputum (gram stain < 25 PMN/LPF)

2) *did not have the three AECB respiratory pathogens (H. influenzae, S. pneumoniae, and M. catarrhalis) isolated from pre-treatment sputum culture*
3) *had a positive chest x-ray*

MCE population will include all MITT patients EXCLUDING those who

4) did not have a test of cure visit
5) *were poorly compliant (received less than 4 days of study drug / <3 days for failures)*
6) *violated protocol*
7) *received another systemic antibiotic during study period.*

This analysis will be presented in the integrated review in conjunction with data from Study 064.
(See Table 16 of the Integrated Review)

Statistical Analyses

Analyses of the pre-treatment characteristics and study medication usage for All Treated, Eligible, and Clinically Evaluable Patients by treatment group, were performed. Prognostic factors were also submitted.

Primary Efficacy Analysis

The primary efficacy assessment was based on the analysis of clinical response in the clinically evaluable subset. Equivalence of gatifloxacin to the control regimen was determined using the 95% confidence interval (CI) around the difference in clinical cure rates (gatifloxacin – azithromycin). The gatifloxacin regimen was considered equivalent to azithromycin if the lower confidence limit was greater than or equal to 15%. An adjusted confidence interval, using the method described by Fleiss, was computed to take into account possible heterogeneity of response by the stratification factor, systemic/inhaled corticosteroid use at randomization.

MO COMMENT: The lower limit of confidence at -15% was agreed upon by the FDA in reference to all submitted gatifloxacin protocols and was used in the original application.
The Fleiss method apparently calculates adjusted confidence limits based on "weighted average of the stratum-specific rate differences, where the inverse of the variance of estimated rate difference within the stratum was used as the weight for the corresponding stratum".

Secondary Efficacy Analysis

Clinical response rates for (1) Eligible patients, (2) All Treated Patients were tabulated. By-patient bacteriologic responses were calculated for (3) Microbiologically Evaluable Patients. Adjusted confidence intervals for each of these comparisons were computed as for the primary analysis. Additional secondary analyses include clinical response rates by (4) pre-treatment pathogen and (5) prognostic factor, (6) eradication rates for primary sputum pathogens isolated pre-treatment, and analysis of the (7) time of improvement and (8) resolution of cardinal symptoms via subject symptom diary.

Relapse rates among the (11) cured Clinically Evaluable Patients who had follow-up at Day +21 to +28 were tabulated. The incidence of new infections among All Treated Patients was compared .

MO COMMENT: *Confidence intervals for differences in cure rates were not stratified by site although randomization was balanced by site. Sponsors also point out that for (7) and (8) secondary analyses, the data were collected from patient diaries and were not edited by BMS. The number of patients with usable data was low and results should be interpreted with caution.*

Safety

All patients who received at least one dose of study medication were evaluated for safety. The frequencies of adverse clinical events were summarized by relationship to study drug and displayed by primary term within the relevant body system, as defined in the COSTART adverse clinical events classification system, which was modified by BMS. Those adverse events that were considered drug related (i.e., certainly,

probably or possibly drug related) were also tabulated by severity. Discontinuations due to adverse events were tabulated.

Changes in laboratory test results were tabulated by test. For patients with normal (Grade 0) pre-treatment laboratory test values, the frequencies of Grade 1, 2, 3, and 4 abnormality during/post-treatment were displayed. For each patient, the most abnormal result for each test was counted. For patients with abnormal (Grades 1, 2, or 3) pre-treatment laboratory test values, the frequencies of worsening to Grade 2, 3, or 4 abnormality during/post-treatment were displayed. For each patient, the worst grade change for each test was counted.

Results

Populations

The study period was from October 1999 to May 2000. A total of 296 patients were enrolled, all in the U.S.; all but 2 patients, both in the azithromycin arm, received at least one dose of study therapy. Thirty-three sites enrolled patients with four investigators each enrolling approximately 10% of the total number of patients. Eleven investigators accrued 4 patients (1.4%) or less. Two hundred and eighty (95%) treated patients were Eligible and 252 (86%) treated patients were Clinically Evaluable. One hundred and forty-seven patients (50%) were Microbiologically Evaluable. The rates of eligibility and evaluability were fairly similar for the most part across sites. [See Table 4]

MO COMMENT: Although only the presence of purulent sputum (as defined by >25 PMNs/LPF) was the criteria used for inclusion in this study, the dataset GRAMSTAIN was analyzed by this reviewer to ensure that the majority of these sputum samples also had <10 epithelial cells and that this quality of the sputum was comparable across the three arms. Out of the 766 samples of sputum, the breakdown by the number of epithelial cells in the sputum was analyzed as follows (Table 1). The two arms of study were similar.

Table 2: Gramstain quality (total samples=766)

# epithelial cells/LPF	*Gatifloxacin*	*Azithromycin*
none	*11*	*9*
<10	*295*	*290*
10-25	*45*	*56*
>25	*11*	*4*

*pre-treatment samples, some patients with duplicate specimens

Table 3 : Significant Protocol Violations, All Enrolled Patients (40 Patients)

	Number of Patients (%)		
Violation	Gatifloxacin N=147	Azithromycin N=149	Total N=296
TOC out of window or done by phone	7 (5)	6 (4)	13 (4)
Less than required pre-tx signs/symptoms	-	5 (3)	5 (3)
No purulent sputum pre-treatment	3 (2)	1 (<1)	4 (1)
No TOC visit	2 (1)	2 (1)	4 (1)
Inadequate dosage	-	3 (2)	3 (1)
Lost to follow-up	3 (2)	-	3 (1)
X-ray evidence of pneumonia pre-tx	1 (<1)	2 (1)	3 (1)
Patient did not take study drug	-	2 (1)	2 (<1)
Consent not obtained in window	-	1 (<1)	1 (<1)
Other antibiotic given	1 (<1)	-	1 (<1)
Possibly treated in previous gatifloxacin trial l	(<1)	-	1 (<1)

*some patients with more than one violation

Significant protocol violations were defined as those that prevented a patient from being clinically evaluable. Forty significant protocol violations occurred (Table above). The one patient with protocol violation related to informed consent had signed the consent sixteen days before the first dose of study drug, well outside the required window. Protocol violations were similar between the gatifloxacin and azithromycin treatment groups. One exception being that the five patients who did not have the required signs/symptoms present at study entry was all from the azithromycin group. The reasons for ineligibility were comparable in both the gatifloxacin and azithromycin arms. Fourteen treated patients were ineligible.

Table 4: Distribution of Patients in Study Population and Reasons for Exclusion

	Number of Patients (%)		
Reasons (All Treated Patients)	Gatifloxacin N=147	Azithromycin N=147	Total N=294
Eligible	142 (97)	138 (94)	280 (95)
Ineligible	5 (3)	9 (6)	14 (5)
Did not have required symptoms at entry	–	5 (3)	5 (2)
No Pre-treatment purulent sputum	3 (2)	1 (<1)	4 (1)
Evidence of Pneumonia on pre-tx X-ray	1 (<1)	2 (1)	3 (1)
Possibly Tx in previous gatifloxacin trial	1 (<1)	–	1 (<1)
Consent not obtained in window	–	1 (<1)	1 (<1)
Clinically Evaluable	127 (86)	125 (85)	252 (86)
Clinically Unevaluable	20 (14)	22 (15)	42 (14)
Ineligible	5 (3)	9 (6)	14 (5)
Post-Tx evaluation out of window or via phone	7 (5)	6 (4)	13 (4)
Insufficient dosage	2 (1)	5 (3)	7 (2)
No post-Tx evaluation	2 (1)	2 (1)	4 (1)
Lost to follow-up	3 (2)	–	3 (1)
Other antibiotic received	1 (<1)	--	1 (<1)
Microbiologically Evaluable	73 (50)	74 (50)	147 (50)

Forty-two treated patients were unevaluable with the two most frequent reasons for being ineligibility and having a TOC visit performed either outside the acceptable window of Day +5 to Day +18, or over the telephone. Two hundred and six (70%) treated patients had a pre-treatment pathogen of which 178 were Clinically Evaluable. Of these patients, one hundred and forty-seven patients were microbiologically Evaluable with a total of 175 Evaluable pathogens.

MO COMMENT: Patients were well balanced between the 2 groups in terms of eligibility, clinical evaluability, and microbiological evaluability. They were also well balanced in terms of reasons for ineligibility and unevaluability. Reviewer agrees with the applicant regarding the ineligibility of 14 patients who did not have required symptoms at entry (5), who did not have a purulent sputum specimen (4), who had evidence of pneumonia on pre-treatment x-ray (3), who were possibly treated in a previous gatifloxacin trial (1), and who did not have timely informed consent (1). These facts were well documented on the case report forms and in the database. (I randomly selected 5 of the 14 case report forms for closer inspection).

Data Sets

The safety data set consisted of All Treated Patients.
The primary data set for analysis of clinical efficacy consisted of the Clinically Evaluable Patients, the primary data set for analysis of bacteriologic efficacy consisted of the Microbiologically Evaluable Patients. The Eligible and All Treated Patients formed secondary efficacy data sets.

Demography and Patient Characteristics

Of the 294 patients treated, 53% were female; the majority (80%) was white and the median age was 52 years (Table below). There were more females in the gatifloxacin (Clinically Evaluable Patients 58% vs. 49%) group; otherwise, the demographics in the gatifloxacin treated patients were similar to the azithromycin-treated patients.

Table 5: Demography, All Treated Patients

Characteristic	Number of Patients (%)		
	Gatifloxacin N = 147	Azithromycin N = 147	Total N = 294
Gender [N (%)]:			
Male	65 (44)	72 (49)	137 (47)
Female	82 (56)	75 (51)	157 (53)
Race [N(%)]:			
White	116 (79)	120 (82)	236 (80)
Black	18 (12)	19 (13)	37 (13)
Hispanic	7 (5)	4 (3)	11 (4)
Other[a]	6 (4)	4 (3)	10 (3)
Age (years):			
Mean	50	53	52
Median	50	54	52
Min - Max	18 - 85	18 - 85	18 - 85
Weight[b] (kg):			
Mean	86.67	83.28	84.97
Median	81.2	82.6	81.6
Min - Max	41 - 167.8	39.9 - 157.8	39.9 - 167.8

a Includes 9 Asian and 1 Native American.

b Weight not recorded for 3 gatifloxacin patients and 2 azithromycin patients.

MO COMMENT: *The demographic characteristics in the two arms are similar for All Treated Patients, Eligible Patients, and Clinically Evaluable Patients. It is unlikely that the imbalance in gender representation between the two groups for the Clinically Evaluable Patients will affect study results given the nature of the disease. As seen in Trial #1, age range is extremely wide spanning 18 years of age to 85 years. However, unlike the age data from the original 064 trial, the mean and median age are higher and reflects similar picture to the dataset when sites 23 and 24 were excluded in the 064 trial.*

Medical History and Presenting Conditions

A wide array of conditions was recorded for medical history with most systems represented. One hundred percent of the patients had a history of any respiratory condition; all had chronic bronchitis in meeting the

definition of chronic cough and sputum production on most days for 3 consecutive months for greater than two consecutive years. A variety of other respiratory conditions were represented as well, including asthma/asthmatic bronchitis in a quarter of the patients and COPD in 15% of the patients.

The number of episodes of AECB that the patients had experienced in the previous 12 months was similar between the two treatment groups; the majority (59%) had 2 or 3 episodes during the previous year.

Within five days of the pre-treatment visit, there were no patients that received any systemic antimicrobials. Corticosteroids were used in one third of the patients at the time of randomization. Prednisone was the sole systemic corticosteroid used (10% of the patients in each treatment arm). Among the various inhaled corticosteroid, Fluticasone was the most commonly used medication (13% of the patients in the gatifloxacin arm and 16% for azithromycin arm).

Except for the five patients in the azithromycin arm who did not have dyspnea and were deemed ineligible for the primary efficacy analysis, all other patients who entered the study had the four required signs/symptoms of an acute exacerbation. Moreover, the majority of patient also presented with additional signs and symptoms associated with acute exacerbation of chronic bronchitis including chest tightness, malaise, and headache. There were no appreciable differences between the treatment groups.

MO COMMENT: *The representation of different medical conditions was well balanced between the 2 groups. It is interesting to note that although inclusion to this second study entailed meeting Type I Anthonisen criteria (and thus implying that these patients were had more "severe" disease) as compared to allowance for Type II patients in the 064 study, the underlying medical condition listed for COPD is actually at 41% for the 064 study and only 15% here in the 065 study. This appears to be inconsistent with the clinical picture and difficult to explain.*

Microbiologic Documentation

A total of 292 pathogens were isolated from 206 (70%) treated patients. One-hundred and thirty-five patients had a single pathogen, while 71 had multiple pathogens. There were 47 isolates of *M. catarrhalis*, 37 isolates of *H. influenzae*, and 27 of *S. pneumoniae*. Generally, each treatment group had similar numbers of each pathogen. Of the *H. influenzae* isolates, there were 6 β-lactamase positives in the gatifloxacin arm and 7 in the azithromycin arm. There were 2 gatifloxacin and no azithromycin patients with penicillin resistant (>2.0 ug/mL) *S. pneumoniae*. Other frequently isolated respiratory organisms included *S. aureus* (54) and *H. parainfluenzae* (46). Sixty-six pathogens of 19 different organisms constituted Gram-negative isolates. Two intermediate and no fully resistant susceptibilites were seen with pre-treatment pathogens with gatifloxacin whereas 84 (29%) pre-treatment isolates were fully resistant to azithromycin.

MO COMMENT: *Although small is numbers. the 3 major pathogens usually involved in AECB (H. influenzae, S. pneumoniae and M. catarrhalis) are well represented in the study. There was also a good proportion of patients with H. parainfluenzae and S. aureus to allow for assessment of efficacy against those organisms.*

Prognostic Factors, All Treated Patients

All patients enrolled in this study were to have had Type I exacerbations by the Anthonisen classification, as defined by the study inclusion criteria. All gatifloxacin patients had Type I, but as previously described, 4 patients in the azithromycin did not have dyspnea at study entry. At the time of randomization, half of the patients had been symptomatic for seven days or less. Half of all patients were current smokers and 78% had a history of smoking. Eighty-seven (30%) patients were receiving either systemic or inhaled corticosteroids at the time of randomization. The number of patients in the two groups was comparable.

MO COMMENT: The two groups were generally similar in terms of exacerbation type, smoking history, current smoking status, duration of current episode of AECB, and pre-treatment corticosteroid use.

Study Therapy

The majority of patients (92%) took all 5 doses of study therapy. Duration of less than 5 doses occurred in 7 (5%) gatifloxacin patients and 11 (7%) of the azithromycin patients. A total of 10 (3%) of patients discontinued gatifloxacin and azithromycin prematurely. Five of these patients (2 in gatifloxacin and 3 in azithromycin groups) discontinued treatment due to adverse events.
One patient in gatifloxacin arm and two in the azithromycin arm discontinued therapy as treatment failures. There were no interruptions of therapy related to clinical findings or laboratory abnormalities that occurred on therapy.

***Reviewer's Comments**: CRFs reviewed: (gatifloxacin: 034-360, 045-266, 002-039, 055-399) and (azithromycin: 008-452, 010-189, 011-054, 011-055). First 3 for gatifloxacin were discontinuations due to adverse events, last one due to early failure. All 4 for azithromycin were listed as adverse events, but my review showed the first one to be early treatment failure (pneumonia).*

Concomitant Therapy

No patient in either the gatifloxacin or the azithromycin arm received systemic concomitant antibacterial. There were two patients in the gatifloxacin group who received topical antimicrobial formulations (tobramycin drops and Vagisil). Thirty-one % of the patients received concomitant corticosteroids with the use of any concomitant corticosteroid comparable in the two treatment groups. Prednisone (10%) was the most frequently prescribed systemic steroid, while fluticasone (15%) was the most frequently prescribed inhaled agent. A total of 231 (79%) patients received a variety of concomitant non-antimicrobial medications. The use of these medications was generally comparable in the two treatment arms.

Post-treatment Therapy

The 46 patients who received systemic antibacterial agents post-treatment (23 in each treatment group) fell into three main groups:

1) Treatment failures who received an alternate antibiotic for AECB: 17 patients in the gatifloxacin arm and 14 in the azithromycin arm;
2) Patients who were treated for new infections: 4 patients in the gatifloxacin arm and 3 in the azithromycin arm;
3) Patients who were cured at TOC visit and relapsed: 2 patients in the gatifloxacin arm and 6 in the azithromycin arm.

Systemic antimicrobials were prescribed with similar frequency in the two treatment arms with other fluoroquinolones (i.e. levofloxacin and ciprofloxacin) being the most frequently prescribed agents.

Efficacy Results

MO COMMENT: Although patients were randomized according to corticosteroid use, confidence intervals were constructed only for the group as a whole and adjusted for corticosteroid stratification using the Fleiss method. (The review team statistician verified this method). The primary efficacy analysis was not done on an intent-to-treat basis; patients who discontinued study drug before receiving 5 days of therapy because of adverse events or worsening of their condition were not considered evaluable and thus were not included in the primary efficacy analysis. The patients were well balanced between the two study groups. The intent-to-treat population would be more closely represented by the All Treated of the Eligible subsets. Thus, analyses of all subsets will be considered by the FDA

The applicant's definition of cure included those patients whose symptoms improved as well as those patients whose symptoms returned to baseline. Although the "improved" assessment did not contain

a grading system, this lack of exactness is offset by the strict definition in the applicant's analytical plan that all four cardinal signs and symptoms had to be at least improved for a response of Cured to be assigned. If two or three were resolved or improved and one was unchanged since the pre-treatment evaluation, this patient was deemed a treatment failure, even if no additional antibiotic therapy was prescribed.

Appendix 4 of this sNDA volume 5 gives 41 instances where the Investigator's evaluation of clinical response differed from the Medical Monitors. The numbers are similar between the two arms and the majority actually went from CURED assigned by the Investigators to FAILURE by the Medical Monitor. There were 19 discrepancies in the gatifloxacin arm and 22 in the azithromycin arm with breakdown as follows:

Table 6: Discrepancies in Response Reassigned

Clinical response reassigned By BMS Medical Monitor	*Gatifloxacin arm Discrepancies (n=19)*	*Azithromycin arm Discrepancies (n=22)*
From Cured to Failure	*10 patients*	*14 patients*
From UTD, NA, or Failure to Cured	*3*	*3*
From UTD, NA to Failure or UTD	*5*	*5*

Although less number of failures were assigned to the gatifloxacin group by the above criteria (23 vs 33 for azithromycin), more patients in the gatifloxacin group (13 vs 9 for azithromycin) were given additional systemic antibiotics. To assure that the patients who were deemed failures were comparable in the severity of signs and symptoms between the two groups, a separate analysis was done by the FDA (see results under section: Clinical Failures) where all treated patients who had at least 2/4 signs and symptoms be improved or resolved and no sign or symptom being worse were included (3 additional patients for CURED in gatifloxacin group and 17 additional patients for CURED in azithromycin group).

Clinical Response; Clinically Evaluable Patients

Cure rates were similar in the two treatment groups as per the applicant's analysis. (gatifloxacin = 82%, azithromycin =74%), 95% CI (-3.4%, 17.0%, Table 7)

Table 7: Clinical Response, Clinically Evaluable Patients (Applicant's analysis)

	Number of Patients (%)		
Clinical Response	Gatifloxacin (N=127)	Azithromycin (N=125)	Total (N=252)
Cure	104 (82)	92 (74)	196 (78)
Failure	23 (18)	33 (26)	56 (22)

***MO COMMENT:** The breakdown of clinically evaluable patients by site showed four sites to have 40% or greater difference in cure rates between the two treatment arms with three of those four sites giving higher cure rate for the gatifloxacin arm. Otherwise, the cure rates in the remaining 29 sites were comparable between the two arms with 10/29 sites having slightly greater cure rates in the gatifloxacin arm. The cure rate overall in the clinically evaluable patient population (applicant's primary efficacy analysis) was slightly higher for the gatifloxacin arm. The lower limit of the 95% CI for this analysis is within the designated limit of -15%.*

Clinical Response; Eligible and All Treated Patients

Table 8: Clinical Response, Eligible Patients (Applicant's analysis)

	Number of Patients (%)		
Clinical Response	Gatifloxacin (N=142)	Azithromycin (N=138)	Total (N=280)
Cure	110 (78)	98 (71)	208 (74)
Failure	32 (22)	40 (29)	72 (26)

95% Confidence Interval for Difference in Cure Rate: (-5.2%, 15.3)

Table 9: Clinical Response, All Treated Patients (Applicant's analysis)

	Number of Patients (%)		
Clinical Response	Gatifloxacin (N=147)	Azithromycin (N=147)	Total (N=294)
Cure	112 (76)	104 (71)	216 (73)
Failure	30 (20)	40 (27)	70 (24)

95% Confidence Interval for Difference in Cure Rate: (-5.8%, 14.2%)

MO COMMENT: *The cure rates by study site for the Eligible Population was similar to the site distribution seen with Clinically Evaluable Patients as discussed above. The lower limits of these two analyses were also within the designated limit of –15%.*

Table 10: Clinical Response by Prognostic Factor; Clinically Evaluable Patients

	Number Cured/Evaluable Patients (%)		
Prognostic Factor/ Subcategory	Gatifloxacin N = 127	Azithromycin N = 125	Total N = 252
Duration of Current Episode			
0 - 7 Days	57/66 (86)	39/56 (70)	96/122 (79)
> 7 Days	46/57 (81)	49/63 (78)	95/120 (79)
Not Recorded	1/4 (25)	4/6 (67)	5/10 (50)
Systemic or Inhaled Corticosteroid Use at Randomization			
Yes	30/38 (79)	25/35 (71)	55/73 (75)
No	74/89 (83)	67/90 (74)	141/179 (79)
Current Smoking Status			
Smoker	51/62 (82)	48/57 (84)	99/119 (83)
Non-Smoker	53/65 (82)	44/68 (65)	97/133 (73)
History of Smoking			
Yes	81/98 (83)	69/97 (71)	150/195 (77)
No	23/29 (79)	23/28 (82)	46/57 (81)

MO COMMENT: *Cure Rates in clinically evaluable patients between the two arms for the above relevant prognostic factors were generally comparable. Gatifloxacin arm had a slightly better cure rate for shorter duration of symptoms at the time of presentation. The other significant difference was seen in the patients who were currently non-smokers. Those on gatifloxacin arm fared better than those in the azithromycin arm. This issue of smokers doing better than non-smokers was more pronounced in study 064 and demography distribution separately analyzed for current smokers and non-smokers in that study. Separate analysis was not performed for 065 study.*

Table 11: Clinical Cure Rates by Pathogen; Clinically Evaluable Patients

Pathogen[a]/Subtype	Number Cured/Number Isolated (%)		
	Gatifloxacin N = 127	Azithromycin N = 125	Total N = 252
Total patients with pathogens	76/91 (84)	65/87 (75)	141/178 (79)
H. influenzae	**10/12 (83)**	**14/18 (78)**	**24/30 (80)**
β-Lactamase +	2/3 (67)	6/7 (86)	8/10 (80)
β-Lactamase -	8/9 (89)	8/11 (73)	16/20 (80)
S. pneumoniae	**7/12 (58)**	**7/10 (70)**	**14/22 (64)**
Penicillin Susceptible	4/5 (80)	7/9 (78)	11/14 (79)
Penicillin Intermediate	3/5 (60)	0/1	3/6 (50)
Penicillin Resistant	0/2	–	0/2
M. catarrhalis	**23/26 (88)**	**11/16 (69)**	**34/42 (81)**
β-Lactamase +	22/25 (88)	11/15 (73)	33/40 (83)
β-Lactamase -	1/1 (100)	0/1	1/2 (50)
H. parainfluenzae	**18/22 (82)**	**14/19 (74)**	**32/41 (78)**
β-Lactamase +	2/2 (100)	–	2/2 (100)
β-Lactamase -	16/20 (80)	14/19 (74)	30/39 (77)
S. aureus	**23/26 (88)**	**21/24 (88)**	**44/50 (88)**
Methicillin Resistant	1/2 (50)	2/2 (100)	3/4 (75)
Methicillin Sensitive	22/24 (92)	19/22 (86)	41/46 (89)
Other Gram-negative[b]	3/3 (100)	5/5 (100)	8/8 (100)
Other Gram-positive[c]	23/31 (74)	17/24 (71)	40/55 (73)

[a] A patient may have had more than one pathogen isolated pre-treatment.

[b] Includes 17 different species.

[c] Includes 4 different species.

The cure rates for Clinically Evaluable patients with at least one pre-treatment sputum pathogen were 84% in the gatifloxacin arm and 75% in the azithromycin arm (95% CI for the difference in cure rates: -5.3%, 18.4%). For four of the 5 major pathogens for this application, namely *H. influenzae*, *M catarrhalis*, *H. parainfluenzae*, and *S. aureus*, the gatifloxacin arm was similar or slightly better in the cure rates over the active control arm. However, for *S. pneumoniae*, gatifloxacin arm had 7/12 cured versus 7/10 for azithromycin arm. Of the 5 patients who were labeled as clinically failed (0-176, 030-233, 030-372, 010-464, 010-464), 3 were not prescribed additional antibiotics (011-176,030-233, 030-372) and two of these three (011-176, 030-372) had actual documentation of eradication of *S. pneumoniae*.

MO COMMENT: Reviewer agrees with the data presented in the above table (adapted from applicant's Table 10.1.1.4). Crt Datasets "Evbaxrsp" and "Culture" were reviewed and the numbers concur with above. The confidence interval for the difference in cure rates of those patients with a pathogen was acceptable. Furthermore, cure rates were comparable for the 5 respiratory pathogens isolated most commonly. The numbers for S. pneumoniae 7/12 cured (58%) in this subset of clinically evaluable patients is somewhat concerning. This low rate of cure may be due to the small numbers of available patients. We will have to look at this number more closely in conjunction with the other study (064) in the integrated analysis.

Microbiologically Evaluable Patients

The clinical cure rates by pathogen for Microbiologically Evaluable patients was 86% in the gatifloxacin arm, 74% in the azithromycin (95% CI for the difference in cure rates: -3.2%, 22.2%). The overall bacteriologic Eradication Rates by pathogen for Microbiologically Evaluable patients were 88% in the gatifloxacin arm and 84% in the azithromycin arm. Both these results, as well as the outcomes by individual pathogens largely paralleled the results seen in the Clinically Evaluable population. Eradication rates for S. pneumonia were 86% (6/7) and 89% (8/9) for gatifloxacin and azithromycin.

Table 12: Eradication Rates by Pathogen; Microbiologically Evaluable Patients

Pathogen	Number Eradicated/No. Isolated (%)		
	Gatifloxacin N = 73	Azithromycin N = 74	Total N = 147
Total	75/88 (88)	69/83 (84)	150/175 (86)
H. influenzae	11/12 (92)	15/18 (83)	26/30 (87)
S. pneumoniae	6/7 (86)	8/9 (89)	14/16 (88)
M. catarrhalis	24/26 (92)	14/16 (88)	38/42 (90)
H. parainfluenzae	18/22 (82)	13/18 (72)	31/40 (78)
S. aureus	16/19 (84)	19/22 (86)	35/41 (85)

MO COMMENT: There were adequate numbers of patients with H. influenzae, M. catarrhalis, S. pneumoniae, H. parainfluenzae or S. aureus for assessment of efficacy. There were insufficient data to show effectiveness against penicillin-intermediate and penicillin-resistant S. pneumonie. Since in so many cases the pathogen eradication rates was presumed, a summary of the dataset "EVBRRSP" was done by this reviewer to assure that comparable numbers of patients were designated as Presumed Eradicated in both arms.

Table 13: Comparison of the Two Arms of Study – Eradication Assignment

Drug	*Eradicated*	*Persisted*	*Presumed Persisted*	*Presumed Eradicated*
Gatifloxacin	*12*	*4*	*7*	*65*
Azithromycin	*10*	*3*	*11*	*63*

Table 14: Bacteriologic Eradication Rates; Eligible Patients (Applicant's analysis)

	Number of Patients (%)		
Pathogen Response	Gatifloxacin (N=148)	Azithromycin (N=130)	Total (N=278)
Eradicated	123 (83)	97 (75)	220 (79)
Failure	25 (17)	33 (25)	58 (21)

The trends in bacteriologic eradication rates for relevant pathogens were similar to those reported for Microbiologically Evaluable Patients. The overall eradication rates in the Eligible population were 83% for gatifloxacin and 75% for azithromycin. There were 14 documented persistent pathogens in the Eligible population, seven in each treatment arm. Three isolates of *S.aureus*, one each of *S. Pneumoniae, E. coli, K. pneumoniae,* and *H. parainfluenzae* consisted of the 7 persistent pathogens in the gatifloxacin arm. In the azithromycin arm, the persistent pathogens included three isolates of *S. aureus*, and one each of *C. diversus, K. pneumoniae, S. marcescens,* and *H. parainfluenzae.*

Clinical Failures

Fifty-six patients had a clinical response of Failure with persistence and/or worsening of primary signs and symptoms as the most frequent reason for being judged a treatment failure.

Table 15: Reason Clinical Response is Failure; Clinically Evaluable Patients

Reason	Number of Patients:	Gatifloxacin (N=127)	Azithromycin (N=125)
Persistence/worsening of primary S & S		20	32
Requires other antibiotic for tx of this acute episode		2	–
New clinical S & S of infection under study		–	1
Patient died of pneumonia		1	–
	Total = 56:	23	33

death narrative to be provided under the safety analysis section

***MO COMMENTS**: Twenty-two (13 gatifloxacin, 9 azithromycin) of the 56 patients who were considered treatment failures were given additional systemic antibiotics, while the other 34 (10 gatifloxacin, 24 azithromycin) patients did not receive additional antibiotics. In other words, 13/23 (56%) patients in the gatifloxacin arm were treated with additional antibiotics while only 9/33 (27%) patients in the azithromycin arm were treated with additional antibiotics. To assure that the patients who were deemed failures were comparable in the severity of signs and symptoms between the two groups at the time of failing therapy, a separate analysis was done where clinically evaluable patients who had at least 2/4 signs and symptoms be improved or resolved and no sign or symptom being worse were included. This analysis in fact added more patients to azithromycin CURE group (3 additional patients for CURE in gatifloxacin group and 17 additional patients for CURE in azithromycin group (see Table 17 below).*

Table 16: Clinical Response, Clinically Evaluable Patients (Applicant's analysis)

	Number of Patients (%)		
Clinical Response	Gatifloxacin (N=127)	Azithromycin (N=125)	Total (N=252)
Cure	104 (82)	92 (74)	196 (78)
Failure	23 (18)	33 (26)	56 (22)

[gatifloxacin = 82%; azithromycin = 74%; 95% CI (-3.4%, 17.0%)]

Table 17: Clinical Response, Clinically Evaluable Patients (FDA's adjusted analysis)

	Number of Patients (%)		
Clinical Response	Gatifloxacin (N=127)	Azithromycin (N=125)	Total (N=252)
Cure	107 (84)	107 (87)	219 (87)
Failure	20 (16)	18 (13)	33 (13)

gatifloxacin = 84%; azithromycin = 87%;
95% CI (BMS CI –13.1, 4.1; regular Fleiss CI –11.5, 5.7)

MO COMMENT: *In this "worst case scenerio" analysis, the adjustment resulted in the observed cure rates being much closer together than in the original analysis, but the lower bounds of the CI's are well within the acceptable 15% limit so the overall conclusions remain the same.*

Relapses

Nine patients (4 in gatifloxacin group and 5 in azithromycin group) with a clinical response of cured at the TOC visit relapsed with AECB at the extended follow-up visit, Day +21 to +28. The overall cure rate at the end of study was 79% in the gatifloxacin arm and 70% in the azithromycin arm.

Table 18: Clinical Response, Clinically Evaluable Patients (Applicant's analysis)

	Number of Patients (%)		
Clinical Response	Gatifloxacin (N=127)	Azithromycin (N=125)	Total (N=252)
Cure at the TOC visit	104 (82)	97 (74)	196 (78)
Late Follow-up Obtained	94 (90)	89 (97)	183 (93)
Sustained cure	90 (96)	84 (94)	174 (95)
Relapse	4 (4)	5 (6)	9 (5)
Cure Rate at End of Study*	100/127 (79)	87/125 (70)	187/252 (74)

MO COMMENT: *The 95% CI for difference in cure rates when relapse patients were taken into account were (-3.1%, 18.4%). The relapse numbers and character were similar between the two arms. Only two pathogens (one patient with MSSA and one patient with Candida) were isolated at the time of relapse.*

New Infections

Twelve patients (4%) developed new infections. The time period included on-study and extended to 30 days after the last dose of study therapy. Among the gatifloxacin patients, there were 9 new infections with 4/9 being sinusitis. Three new infections were listed for the azithromycin group.

Table 19: New Infections; All Treated Patients (Applicant's analysis)

	Number of Patients (%)		
Diagnosis	Gatifloxacin (N=147)	Azithromycin (N=147)	Total (N=294)
Sinusitis	4 (3)	1 (<1)	5 (2)
Vaginits	2 (1)	–	2 (1)
Dental Abscess	1 (<1)	–	1 (<1)
Candidiasis	1 (<1)	–	1 (<1)
Gastrointestinal Inflammation	1 (<1)	–	1 (<1)

Respiratory	–	1 (<1)	1 (<1)
Strep Throat	–	1 (<1)	1 (<1)
Number of Patients Reporting New	**9 (6)**	**3 (2)**	**12 (4)**

MO COMMENT: *The number of new infections was low and comparable between the 2 groups, with no life-threatening infections noted. It is interesting to note that 5/12 new infections (and 4 of those 5 being in the gatifloxacin arm) were sinusitis. The clinical significance of this finding is currently unclear.*

Safety Evaluation

All Adverse Clinical Events

Adverse clinical events of all causes were slightly more frequent in gatifloxacin (73 patients) than azithromycin (66 patients). In both groups, approximately half were not considered drug-related according to the investigators. The most frequent events overall were respiratory, which were generally attributed to the underlying disease. The next most frequent events were gastrointestinal in nature.

Drug-related Adverse Clinical Events

The incidence of adverse clinical events assessed by the investigator to be related to gatifloxacin was 19% (28 patients) compared to 14% (20 patients) on azithromycin (Table)
Nausea, abdominal pain, and diarrhea were the most frequent drug-related events reported in both treatment arms. In both arms, the majority of events were reported as mild or moderate in severity. There were four adverse events reported as severe, three events in the gatifloxacin arm and one in the azithromycin arm. In the gatifloxacin arm, patient 004-002 developed diarrhea and vaginal yeast infection that were both severe in nature. Another patient, 030-022, also developed symptoms of severe vaginal yeast infection while on treatment. In the azithromycin-treated group, patient 034-288 developed allergic dermatitis that was judged to be severe. One patient 004-077 treated with gatifloxacin had an adverse event judged to be very severe. He developed right buttock spasms two days after finishing his 5 day course of therapy. The symptom was reported as very severe 3 weeks later, but did not require treatment as per the applicant.

Table 20: All Adverse Clinical Events

Number of Patients (%):	Gatifloxacin (N=147)			Azithromycin (N=147)		
Adverse Clinical Events	DR	NDR	Total	DR	NDR	Total
Coughing	–	12 (8)	12 (8)	–	8 (5)	8 (5)
Increased Sputum	1 (<1)	9 (6)	11 (7)[a]	–	6 (4)	6 (4)
Rhinitis	–	11 (7)	11 (7)	–	8 (5)	8 (5)
Bronchitis	–	8 (5)	8 (5)	–	3 (2)	3 (2)
Diarrhea	4 (3)	4 (3)	8 (5)	10 (7)	5 (3)	15 (10)
Dyspnea	–	8 (5)	8 (5)	–	7 (5)	7 (5)
Headache	2 (1)	6 (4)	8 (5)	3 (2)	6 (4)	9 (6)
Chest Pain	–	7 (5)	7 (5)	–	8 (5)	8 (5)
Nausea	6 (4)	1 (<1)	7 (5)	3 (2)	1 (<1)	4 (3)
Abdominal Pain	5 (3)	–	5 (3)	4 (3)	1 (<1)	5 (3)
Pharyngitis	1 (<1)	4 (3)	5 (3)	1 (<1)	5 (3)	6 (4)
Back Pain	–	4 (3)	4 (3)	–	2 (1)	2 (1)
Dizziness	3 (2)	1 (<1)	4 (3)	3 (2)	1 (<1)	4 (3)
Flatulence	4 (3)	–	4 (3)	–	–	–
Vaginitis	4 (5)[b]	–	4 (5)[b]	–	–	–
Abnormal Breath Sounds	–	2 (1)	3 (2)[a]	–	2 (1)	2 (1)
Dry Mouth	3 (2)	–	3 (2)	–	–	–

Infection	–	3 (2)	3 (2)	–	1 (<1)	1 (<1)
Insomnia	2 (1)	1 (<1)	3 (2)	–	2 (1)	2 (1)
Lacrimal disorder	–	2 (1)	3 (2)[a]	–	–	–
Sinusitis	–	3 (2)	3 (2)	–	2 (1)	3 (2)
Chills	–	2 (1)	2 (1)	1 (<1)	5 (3)	6 (4)
Flu Syndrome	–	2 (1)	2 (1)	–	3 (2)	3 (2)
Nervousness	1 (<1)	1 (<1)	2 (1)	–	3 (2)	3 (2)
Pain	–	2 (1)	2 (1)	–	5 (3)	5 (3)
Arthralgia	1 (<1)	–	1 (<1)	2 (1)	1 (<1)	3 (2)
Malaise	–	1 (<1)	1 (<1)	–	7 (5)	7 (5)
Vomiting	–	1 (<1)	1 (<1)	2 (1)	1 (<1)	3 (2)
Total Events	37	95	132	29	93	122
Patients with Any Adverse Clinical Event	**28 (19)**	**44 (30)**	**73 (50)**	**20 (14)**	**46 (31)**	**66 (45)**

[a] add 1 event to total for Not Recorded; [b] Percent based on 82 gatifloxacin-treated females
DR = Drug Related; NDR = Not Drug Related

Table 21: Drug-related Adverse Clinical Events

Number of Patients (%):	Gatifloxacin (N=147)				Azithromycin (N=147)			
Adverse Clinical Events	Mild	Mod	Severe	Total	Mild	Mod	Total
Nausea	5 (3)	1 (<1)	–	6 (4)	1 (<1)	2 (1)	3 (2)
Abdominal Pain	3 (2)	2 (1)	–	5 (3)	2 (1)	2 (1)	4 (3)
Diarrhea 2 (1)	1 (<1)	1 (<1)	4 (3)	7 (5)	3 (2)	10 (7)	
Flatulence	4 (3)	–	–	4 (3)	–	–	–
Vaginitis	1 (1)	1 (1)	2 (2)	4 (5)[a]	–	–	–
Dizziness	2 (1)	1 (<1)	–	3 (2)	2 (1)	1 (<1)	3 (2)
Dry Mouth	2 (1)	1 (<1)	–	3 (2)	–	–	–
Headache	2 (1)	–	–	2 (1)	2 (1)	1 (<1)	3 (2)
Patients with Any Adverse Clinical Event	**15 (10)**	**10 (7)**	**2 (1)**	**28 (19)[b]**	**10 (7)**	**9 (6)**	**20 (14)[c]**

[a] Percentage based on 82 gatifloxacin-treated females; [b] Includes 1 very severe event;
[c] Includes 1 severe event; Mod = Moderate

MO COMMENT: *Most adverse events in the gatifloxacin group were non-serious in nature. Nausea was most frequent with gatifloxacin, and diarrhea with azithromycin. The incidence of dizziness was comparable. Vaginitis occurred in gatifloxacin group but not in the azithromycin group. Quinolone-class related events, namely phototoxicity, tendinitis, seizures, and cardiac symptoms, were not encountered.*

Deaths and Serious Adverse Events

There was one death during the study period.

"Patient 051-420 was a seventy-five year-old male with a past medical history of BPH and 'stable leukemia', for which he was not receiving treatment. At the time of his randomization to gatifloxacin on 14 April 2000, his white blood cell count was 52,000, with 15% neutrophils and 82% lymphocytes. His pre-treatment sputum culture was positive for *S. marcescens*. He completed therapy on 18 April and reported improvement in all four cardinal signs and symptoms during the telephone contact on 21 April. When he missed his next scheduled appointment on 27 April, several unsuccessful attempts were made to reach him. On 4 May, the patient's wife phoned the site to inform study staff that the patient had been admitted to the hospital on 27 April with pneumonia, and had died that same day of respiratory failure and cardiac arrest. An autopsy was not performed" (taken from page 123, volume 5 of the Supplemental NDA).

There were 20 serious adverse events in 14 (5%) patients (7 in each treatment arm) during the study period. None of these events were judged to be study drug-related according to the investigators. Nine patients (5 in gatifloxacin arm and 4 in the azithromycin arm) had serious adverse events that were respiratory in nature (hospitalizations for pneumonia, asthma, or worsening exacerbation). One other gatifloxacin-treated patient with serious adverse event was hospitalized for back pain and the last patient was hospitalized with chronic pelvic pain. The three other patients in the azithromycin arm with serious adverse events were hospitalized for detoxification, for cholelithiasis, and for gastroesophageal reflux induced chest pain.

MO COMMENT: *Brief case summaries of these fourteen patients (002-039, 011-174, 012-231, 018-198, 045-261, 045-266, 051-420, 010-189, 010-193, 011-173, 018-058, 018-320, 030-235, 041-137) were reviewed. Case 051-42 and randomly selected 5/13 case report forms were reviewed. I agree with the applicant's assessments that these serious adverse events including the one death case above (limited information provided however) are most likely unrelated to the drug trial at hand. Also, this was a low incidence of serious adverse events and both treatment groups were similar.*

Adverse Events Leading to Discontinuation of Study Therapy

Of the 294 patients who received at least one dose of either study drug, six (2%) discontinued treatment due to adverse clinical events. Two patients in the gatifloxacin arm had 6 adverse events altogether. These events were chest pain, dry mouth, dyspnea, confusion, bronchitis, and flu-syndrome. Only one event, dry mouth, was considered to be possibly drug-related. Four patients in the azithromycin arm had a total of eight adverse events. Most events were gastrointestinal in nature (abdominal pain, diarrhea, enlarged abdomen, nausea, vomiting) and 5 of these events were assessed to be possibly drug-related.

MO COMMENT: *The narrative summaries on these 6 patients (034-360, 045-266, 008-452, 010-189, 011-154, 011-055) as well as the corresponding case report forms were reviewed. I agree with the assessments as written by the applicant. Very little percentage of the study population discontinued drug and the reasons for discontinuation were mainly unrelated to the study medication. From this study, it appears that gatifloxacin has a favorable clinical adverse event profile.*

Laboratory Test Results

Patients with Normal Pre-treatment Values

Very few patients with normal baseline values developed abnormal laboratory test results during or post-treatment. There were no appreciable differences between the treatment arms. When abnormalities were present, they were minimal and mild. Hyponatremia was the most frequent abnormality in both treatment arms. Grade 1 hyponatremia was noted in 8 (8%) of 104 tested patients in the gatifloxacin arm and 10 (9%) of 121 in azithromycin arm; Grade 1 AST abnormalities were noted in 6 (5%) of 113 tested patients in the gatifloxacin arm; Grade 1 bicarbonate abnormalities were noted in 11 (3 decreased and 8 increased = total 11%) of 98 tested patients in the azithromycin arm; Grade 1 hyperglycemia were noted in 4 (25%) of 16 tested patients in the gatifloxacin arm.

Grade 3 or Grade 4 laboratory test elevations did not occur in gatifloxacin-treated patients. One case of Grade 3 abnormality occurred in the azithromycin arm.

Patients with Abnormal Pre-treatment Values

Patients who had abnormal (Grade 1, 2, or 3) pre-treatment laboratory values occasionally experienced worsening to a higher grade during or post-treatment. In the gatifloxacin arm, two patients worsened to a Grade 3 abnormality. One patient's bilirubin level went up from 1.3 at entry to 2.2 on Day +9 (without abnormality in transaminases) and was stable at 2.1 on Day +38. Another patient entered the study with a chloride of 92 mEq/L, which went down to 86 on Day +7 and returned to baseline of 92 on Day +57. In the azithromycin arm, one patient developed two Grade 3 abnormalities (AST and ALT) which both returned to baseline by Day +68. Two patients, one on each arm, developed Grade 4 elevation in serum glucose. Both patients were diabetic and both elevations to Grade 4 (310 to 524 mg/dL – gatifloxacin patient and 154 to 516 mg/dL – azithromycin patient) did not have a follow-up level recorded.

MO COMMENT: Overall, gatifloxacin appears to have a favorable adverse event profile in terms of laboratory parameters. One adverse event which may need to be better monitored in future trials is blood sugar levels, especially in light of post-marketing adverse event reports of significant hyperglycemic and hypoglycemic events (see Appendix 3). Abnormalities in liver function tests were not severe.

Conclusions

The applicant's overall conclusions were

1) "results of this study indicate that a five day course of gatifloxacin 400 mg once daily, is safe and effective for the treatment of acute exacerbation of chronic bronchitis"

MO COMMENT: Data in this study were well represented in tables and appendices in hard copy and electronic format, which allowed easy derivation for the reviewers' own analysis. Individual patient data were well documented on Case Report Forms, as shown by a thorough review of 10% of the forms. The primary efficacy analysis between the 5 day gatifloxacin and the comparator azithromycin are well within the lower boundary of the 95% Confidence Interval of –15%. This equivalence in efficacy has shown consistency across different treated populations including the All Treated and Clinically Evaluable patients.

2) " The drug demonstrated a favorable safety profile and clinical and bacteriologic efficacy in a highly representative cohort of patients with this disease compared to azithromycin"

MO COMMENT: The drug demonstrates a favorable safety profile in this study. Certainly, there are no appreciable differences in the safety profile when compared to the active control. Inclusion criteria for this study utilized the Anthonisen classification, which has not been validated to capture the "highly representative cohort of patients with AECB". The classification scheme is entirely clinical, and does not take into account factors such as older age, baseline respiratory medications, pulmonary function tests for assessment of chronic obstructive lung disease, etc. Consequently, when the characteristics of the study population are examined, this reviewer has observed that there was a wide mix of patients. Patients ranged from 18 year old smokers not on any chronic medications most likely having smoke-related cough, to 85 year old medically fragile chronic obstructive pulmonary disease patients routinely treated with oxygen therapy and respiratory medications. It is the latter type of patient developing an acute bacterial respiratory infection who would most benefit from broad-spectrum antimicrobial therapy. So the statement "highly representative" is debatable.

This reviewer agrees that this study demonstrates equivalent bacteriologic efficacy when compared to azithromycin. For the most part, data regarding microbiologic efficacy of gatifloxacin were supportive of effectiveness against the major pathogens involved in AECB, namely H. influenzae, M. catarrhalis, and S. pneumoniae, but also against H. parainfluenzae and S. aureus as compared to azithromycin. However, the cure rate for S. pneumoniae was 7/12 (58%) cured in the subset of clinically evaluable patients. This is somewhat concerning and maybe due to the small number of available patients with this pathogen. Hence, we will have to look at the bacteriologic efficacy of gatifloxacin against this important pathogen in conjunction with study 064 in the integrated analysis.

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